REMARKS

FORMAL MATTERS

Claims 1 and 80-126 are pending after entry of the amendments set forth herein.

Claims 1 and 80-84 were examined and were rejected.

Solely to expedite prosecution, Claim 1 is amended for clarity, and to specify that the rheology modifier is IPM, ethyl oleate, dimethyl phthalate, benzyl benzoate, or a caprylic/capric triglyceride. Claim 80 is amended to recite "from about 1 to about 8.6 weight percent," support for which is found throughout the specification, see e.g., page 20, lines 25-26. Claim 82 is amended to specify components of CAB, support for which is found throughout the specification, see e.g., Table 2 and claim 8, as filed. Claims 80-84 are further amended for clarity.

New claims 85-126 are presented.

Support for new claims 85, 102 and 117 directed to the rheology modifier IPM is found throughout the specification, e.g., at page 26, paragraph 2.

Support for new claims 86, 104 and 118 directed to the solvent triacetin is found throughout the specification, e.g., at page 12, line 20.

Support for new claims 87, 98, 99, 114 and 115 that further specify the network former is found throughout the specification, e.g., at page 12, lines 23-31.

Support for new claims 88 that further specifies amounts of components is found throughout the specification, e.g., at page 12, lines 12-14 and page 20, lines 13-17.

Support for new claims 89-90, 93, 105-106, 109, 119-120 and 123 that further specifies the drug is found throughout the specification, e.g., at page 2, lines 9-10.

Support for new claims 91-92, 107-108 and 121-122 directed to the solvent triacetin is found throughout the specification, e.g., at page 2, lines 24-25 and page 19, line 8.

Support for new claims 94, 110 and 124 that further specify the stimulant is found throughout the specification, e.g., at page 3, line 19.

Support for new claims 95, 96, 111, 112, 125 and 126 directed to capsules is found throughout the specification, e.g., at page 15, lines 20-21.

Support for new claims 97 and 113 that specifies a solvent in which the network former is soluble is found throughout the specification, e.g., at page 9, lines 6-9 and claim 1.

Support for new claims 100 and 116 that specifies components of the CAB is found throughout the specification, e.g., at Table 2 and claim 8, as filed.

New claim 103 is directed to the solvents recited in claim 84.

Accordingly, no new matter is added.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

INTERVIEW SUMMARY

Applicants express their gratitude to Examiner Fubara and Examiner Kwon for the in-person interview conducted on November 23, 2010. The undersigned attended the interview, along with Jean Liu and Neil Verity, both of Durect Corporation.

The rejections of record and proposed amendments were discussed during the interview. In particular, the rejection of the claims under §103(a) based on Tipton was discussed at length. Arguments presented during the interview are presented here.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION

The Office Action stated that claim 80 was rejected because the recitation of "1-8.6%" was not envisioned at the time of filing. Solely to expedite prosecution, claim 80 is amended to recite "from about 1 to about 8.6 weight percent," as suggested by the Examiner.

Applicants submit that the rejection of claim 80 under 35 U.S.C. § 112, first paragraph has been adequately addressed in view of the amendment presented herein. The Examiner is thus respectfully requested to withdraw the rejection.

REJECTION UNDER 35 U.S.C. § 103(A)

The Office Action stated that claims 1 and 80-84 are unpatentable over Tipton *et al.* (U.S. Patent No. 5,747,058). Applicants respectfully traverse the rejection. Without any intention to acquiesce to this rejection and solely to expedite prosecution, claims 1, 80 and 82 are amended. To the extent that this rejection may be applied to the claims as amended and/or newly presented herein, this rejection is respectfully traversed.

Overview of the Pending Claims

The following three independent clams are pending after entry of the present amendment are generally as follows:

1. An oral formulation comprising:
a drug;
sucrose acetate isobutyrate (SAIB);
a network former;
a rheology modifier selected from the group consisting of isopropyl myristate (IPM), ethyl oleate, dimethyl phthalate, benzyl benzoate, and a caprylic/capric triglyceride; and
a solvent.

97. An oral formulation comprising:
a drug;
sucrose acetate isobutyrate (SAIB);
a network former;
a rheology modifier; and
a solvent in which the network former is soluble.

113. An oral formulation comprising:
a drug;
sucrose acetate isobutyrate (SAIB);
a network former;
a rheology modifier selected from the group consisting of isopropyl myristate (IPM), ethyl oleate, dimethyl phthalate, benzyl benzoate, and a caprylic/capric triglyceride; and
a solvent in which the network former is soluble.

Claims 80-96 depend from claim 1. Claims 98-112 depend from claim 97. Claims 114-126 depend from claim 113.

The §103(a) rejection

In maintaining the §103(a) rejection, the Examiner asserts that Tipton teaches compositions including SAIB, CAB and solvent that can optionally include oils and fatty acid esters. The Examiner acknowledges that Tipton does not explicitly teach the claimed formulation.[1]

[1] See Final Office Action, page 6, lines 5-7.

Overview of Applicants' Argument

Applicants submit that relying upon Tipton to maintain an obviousness rejection under §103(a) is not supported by the case law for at least the following reasons:

1) **Tipton's broad disclosure provides no guidance to select the claimed combination**

As discussed in more detail below, Tipton discloses a huge genus of compositions, and does not provide guidance to make an oral formulation as required by the present claims.

2) **Modification of Tipton's disclosed oral formulation to arrive at the claimed elements would render Tipton's disclosed oral formulation *unsatisfactory for its intended purpose***

The disclosed oral formulation of Tipton is a mouthwash, which is provided as an emulsion.[2] An emulsion is defined by Tipton as "dispersions of one liquid in another".[3] Furthermore, Tipton discloses that water is an "essential component" of this mouthwash.[4] Modification of Tipton's mouthwash to include a network former as required by the present claims would render Tipton's mouthwash unsatisfactory for its intended purpose.

3) **Tipton teaches away from adding a lipophilic substance such as a rheology modifier to Tipton's formulations containing CAB or CAP to increase the drug release rate**

Tipton shows addition of CAB[5] or CAP[6] *reduces agent release rate* from a SAIB-containing formulation. As discussed in more detail below, Tipton's data shows that relatively low amounts of drug are released within about 12 hrs to 24 hrs (the time period relevant for oral delivery) when CAB or CAP are present in a SAIB-containing formulation. Tipton teaches that adding a lipophilic substance would *further* decrease drug release rate. Tipton thus *teaches away* from adding a lipophilic rheology modifier to a SAIB-network former composition to provide certain of Applicants' claimed oral formulations.

4. **Applicants' claimed formulation produces unexpected results not disclosed or contemplated by Tipton**

[2] Tipton at col. 11, lines 16-21.

[3] Tipton at col. 1, lines 60-65.

[4] Tipton at, e.g., col. 12, lines 51-53.

[5] CAB is cellulose acetate butyrate.

[6] CAP in Tipton is cellulose acetate proprionate.

Applicants' Argument

The details in support of Applicants' positions are set out in detail below.

1) Tipton's broad disclosure provides no guidance to select the claimed combination

The Tipton reference is a very broad disclosure of a huge genus of compositions. Examples of these enormous and different genera include:

- *Genera encompassing different forms of formulations*

For example, the formulations can be injectable, topical, inhalable (aerosol), oral, rectal, vaginal, nasal, surgical adhesions, scaffolding, void-filling, tissue adhesive;[7]

- *Genera encompassing different uses of formulations*

For example, Tipton discloses the formulations can be applied for use in human pharmaceuticals, veterinary formulations, structural applications (e.g., void filling, scaffolding, tissue regeneration) and insecticide delivery.[8]

- *Genera encompassing numerous different combinations of components.*

For example, Tipton discloses formulations having HVLCM (e.g., SAIB) alone[9] as well as HVLCM and drug. [10]

- *Genera encompassing a multitude HVLCM formulations that can include various optional additives of different classes*[11]

Examples of optional additives include biodegradable polymers, nonbiodegradable polymers, oils and fats, carbohydrates, surfactants, and solvents. Further, Tipton discloses a SAIB/water mouthwash emulsion that can *optionally* include a surfactant, a cosurfactant, an oily component[12] and other additives.[13]

Nowhere does Tipton explicitly teach or suggest a formulation including a drug, SAIB, a network former, a rheology modifier and a solvent, as claimed. The passages of Tipton cited by the

[7] See, e.g, Tipton at col. 10, lines 39-63.

[8] See, e.g, Tipton at col. 10, lines 39-63.

[9] Tipton at cols. 5-6.

[10] Tipton at cols. 6-8.

[11] Tipton at cols. 9-11.

[12] Tipton at col. 11, lines 10-13.

[13] Tipton at col. 12, lines 65-68.

Examiner merely provide laundry lists of possible ingredients that teaches a huge multitude of possible combinations. The Examiner has pointed to no teachings of Tipton that explicitly teach or suggest the claimed combination of ingredients. As such, Applicants submit that Tipton's broad disclosure is not sufficient to render the claimed invention obvious, as set forth by the courts.[14]

As such, Tipton fails to render the claimed invention obvious because Tipton teaches a broad genus and provides no guidance to select the claimed formulation.

2) Modification of Tipton's oral formulation would render it unsatisfactory for its intended purpose

As set forth by MPEP § 2143.01, "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification."[15]

The only specific oral formulation of Tipton, which is described as a "Topical Oral Delivery composition"[16] is an emulsion to be used as a mouthwash.[17] Specifically, Tipton states[18]

> For example, an emulsion of HVCLM/substrate in water can be provided. A useful emulsion falling within this invention is a mouthwash, in which the substrate is an active agent for the treatment of halitosis, oral infections, or other oral disorders.

and[19]

> This invention can be used, for example, to formulate a long-acting mouthwash containing SAIB and an active agent in a water based second carrier material in emulsion form.

[14] A prior art reference that discloses a genus does not inherently disclose all species. "An invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004); see also MPEP §2112. In establishing a prima facie case of obviousness hindsight is not permissible See, e.g., MPEP §2141.01.

[15] MPEP §2143.01, citing *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

[16] Tipton at cols. 11-13.

[17] Tipton at col. 11, lines 16-21.

[18] Tipton at col. 3, lines 55-59.

[19] Tipton at col. 11, lines 16-21.

An emulsion is defined by Tipton as "dispersions of one liquid in another".[20] Furthermore, Tipton explicitly teaches that water is an essential component of a mouthwash:[21]

> Water
>
> Another essential component of the formulations of the mouthwash is water. The formulations of the present inven-

(emphasis added)

Modification of Tipton's mouthwash to include a network former as required by the present claims would render Tipton's mouthwash unsatisfactory for its intended purpose. Network formers of the present claims are, by definition, compounds that "form a network structure when introduced into a liquid medium."[22] Network formers include compounds that are particulate,[23] as well as compounds that "upon exposure to an aqueous environment . . . , form a three dimensional network within the formulation", forming a "skin or surface layer of precipitated network former at the interface between the dosage form and the aqueous environment . . .".[24]

Addition of a network former to the mouthwash of Tipton, which network former is either particulate or becomes particulate due to precipitation following exposure to water would result in composition that is no longer an emulsion, but instead a "lumpy" suspension. Indeed, Tipton teaches that water is an *essential* component of his emulsion. It would be particularly nonsensical for the ordinarily skilled artisan to modify a water-based emulsion with a compound that would simply precipitate upon contact with water for Tipton's intended purpose of a mouthwash.

The Office's suggested modification of Tipton's mouthwash to include a network former such as CAB would render Tipton's mouthwash unsuitable for its intended purposes. CAB would precipitate when contacted with the water of the emulsion-based mouthwash, rendering the mouthwash unsuitable for its intended purpose.

In summary, if the mouthwash of Tipton were modified to include a network former as required by the present claims, the mouthwash would no longer be an emulsion of one liquid dispersed in

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[20] Tipton at col. 1, lines 60-65, which states "Emulsions are defined as dispersions of one liquid in another, stabilized by an interfacial film of emulsifiers such as surfactants and lipids.

[21] Tipton at col. 12, lines 51-53.

[22] Specification at, e.g., page 8, last paragraph.

[23] Specification at, e.g., page lines 2-4 (stating "particles such as silicon dioxide, ion exchange resins, and/or fiberglass").

[24] Specification at page 10, lines 8-11.

another. Instead, the mouthwash would contain particulates. Modification of Tipton's mouthwash would render it unsatisfactory for its intended purpose.

For at least this reason, withdrawal of the rejection of the claims is respectfully requested.

3. Tipton teaches away from including a lipophilic substance such as a rheology modifier to Tipton's CAB-containing compositions

As set forth by the Federal Circuit, the "predictable result" discussed in KSR refers not only to the expectation that prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose. "**An inference that a claimed combination would not have been obvious is especially strong where the prior art's teachings undermine the very reason being proffered** as to why a person of ordinary skill would have combined the known elements"[25] (emphasis added).

The Office has attempted to support the obviousness rejection of the claims by arguing that it would be obvious to modify Tipton's CAB-containing or CAP-containing formulations to include IPM to arrive at the oral formulation of the claims.

This rationale is directly contrary to the teachings of Tipton itself. Specifically, an ordinarily skilled artisan who wished to make an oral formulation would be *directed away* from additional of a lipophilic additive based on the teaching of Tipton.

As set out in the specification, the time of transit of an oral dosage form through the GI tract of a subject is about 8 to 24 hrs.[26] If drug is not released from the dosage form before it exits the GI tract, then the patient does not receive the benefit of the dosage form.

Tipton shows that adding a network former such as CAB or CAP **reduces agent release rate** from SAIB-containing formulations. Tipton's data shows that relatively low amounts of drug are released within about 12 hrs to 24 hrs (the time period relevant for oral delivery) when CAB or CAP is present in a SAIB-containing formulation.

[25] *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.* 567 F.3d 1314 (Fed. Cir. 2009).

[26] Specification at page 15, lines 2-4.

For example, Figures 1 and 11 of Tipton show that addition of CAB or CAP to SAIB resulted in a decrease in the rate of release of an agent. Further, Figure 4 shows that increasing CAB or increasing CAP results in a decrease in the release rate of an agent.

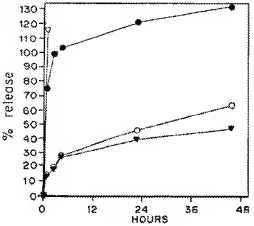

FIG. 1

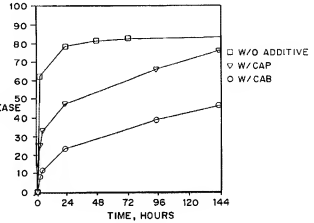

FIG. 11

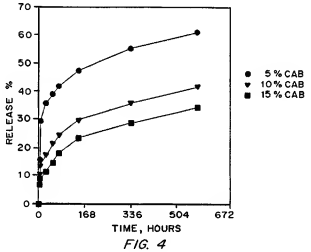

FIG. 4

In Tipton's examples, over the time period of about 12-24 hours (the relevant period for drug release in an oral dosage form), the addition of CAB to Tipton's formulation decreased release rates at 24 hrs to about 35% (see Fig. 1), 25% (Fig. 11), or ~10-30% (Fig. 4).

Tipton teaches that adding a lipophilic substance would *further* decrease drug release rate. Specifically, Tipton states:[27]

> The composition optionally includes additives that modify the properties of the composition as desired. Non-limiting examples of suitable additives include biodegradable polymers, non-biodegradable polymers, natural or synthetic oils, carbohydrates or carbohydrate derivatives, inorganic salts, BSA (bovine serum albumin), surfactants, and organic compounds, such as sugars, and organic salts, such as sodium citrate. In general, the less water soluble, i.e., more lipophilic, the additive, the more it will decrease the rate of release of the substrate, compared to the same composition without the additive. In one embodiment, it is desirable to use additives that increase properties such as the strength or the porosity of the composition. In one embodiment, the HVLCM or LVLCM is used in combination with an additive and without a substrate to be delivered.

As such, Tipton teaches that addition of lipophilic additives such as the cited fats and oils *would further decrease the release rate of drug from Tipton's formulation*. In view of the already low levels of drug released from Tipton's CAB-containing and CAP-containing SAIB formulations as discussed above, Tipton thus *teaches away* from adding a lipophilic rheology modifier to a SAIB-network former composition to provide the claimed oral formulation. The ordinarily skilled artisan would be taught by Tipton that the drug release rates would decrease *even further*, thus providing for even less drug release within the time period relevant for an oral dosage form. Stated differently, if one wanted to increase release of drug from a SAIB-containing composition containing a network former, Tipton teaches that adding a lipophilic additive would make the problem to be solved worse.

Amended Claim 1 (as well as, for example, dependent claims 85, 101, and 102 and independent claim 113) recites a formulation that includes a rheology modifier that is lipophilic. Each of the rheology modifiers recited in claim 1 are lipophilic. As such, one of ordinary skill in the art would not modify the SAIB/CAB-containing and/or SAIB/CAP-containing compositions of Tipton to include a lipophilic rheology modifier, as suggested by the Examiner, since Tipton teaches this would further decrease the drug release rate from the SAIB-containing composition.

Accordingly, for at least this reason, the rejection of claims reciting a rheology modifier that is lipophilic should be withdrawn.

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[27] Tipton at col. 3, lines 30-44.

4. Applicants' claimed formulation produces unexpected results not disclosed or contemplated by Tipton

Applicants also note that, as discussed in detail in prior responses, the claimed compositions provide for abuse deterrence. The claimed oral formulations compositions can provide for unexpected results neither disclosed nor contemplated by Tipton, e.g., oral formulations resistant to quick or rapid extraction to drug in vitro while still providing for controlled release of drug after administration.

Summary

In summary, the teaching of Tipton fails to render the claimed invention obvious because:

1) Tipton's broad disclosure provides no guidance to select the claimed combination of ingredients;

2) Modification of Tipton's disclosed oral formulation by addition of a network former to arrive at the claimed formulation would render Tipton's formulation unsatisfactory for its intended purpose; and

3) Tipton teaches away from including a lipophilic substance such as certain specified rheology modifiers taught by Applicants to Tipton's CAB- or CAP-containing compositions; and

4) Applicants' claimed formulation produces unexpected results not disclosed or contemplated by Tipton.

Applicants submit that the rejection of claims 1 and 80-84 under 35 U.S.C. § 103(a) has been adequately addressed in view of the remarks set forth above. Moreover, Applicants assert that the rejection is also not applicable to the claims newly presented here.

The Examiner is thus respectfully requested to withdraw the rejection.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number DURE-050.

Respectfully submitted,
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Date: December 16, 2010

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